REMARKS

I. Status of the Claims

Claims 1-26 are pending in this application. Claims 11 and 22-26 have been withdrawn from consideration as allegedly being drawn to a nonelected invention.

Applicants propose to amend independent claims 1-7 by moving the phrase "an amino acid selected from SEQ ID NOs. 83-108," by inserting "the" before the recited exo motifs, and by replacing "another" with "an." The proposed amendment does not introduce new matter.

Applicants respectfully request that the Examiner enter this Amendment under 37 C.F.R. § 1.116, placing the pending claims in condition for allowance. Applicants submit that the proposed amendment of claims 1-7 do not raise new issues or necessitate the undertaking of any additional search of the art by the Examiner. Therefore, this Amendment should allow for immediate action by the Examiner. Furthermore, the proposed amendment would place the claims in better form for appeal, should an appeal be necessary.

II. Rejections Under 35 U.S.C. §112, First Paragraph

A. The Specification Provides Written Description Support for the Pending Claims

The Office rejects claims 1-10 and 12-21 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that is not described in the specification so as to reasonably convey to the person skilled in the art that Applicants were in possession of the claimed invention at the time the application was filed. Office Action at page 4. Applicants respectfully traverse this rejection.

A description as filed is presumed to be adequate, unless and until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut that presumption. *See In*

re Marzocchi, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971); *see also*, M.P.E.P. § 2163.04. The burden is on the Office to establish a prima facie case of unpatentability by a preponderance of the evidence. *Id.*

In rejecting a claim, the Office must set forth express findings of fact which support the lack of written description conclusion. M.P.E.P. § 2163.04. These findings should:

(A) Identify the claim limitation(s) at issue; and

(B) Establish a *prima facie* case by providing reasons why a person skilled in the art at the time the application was filed would not have recognized that the inventor was in possession of the invention as claimed in view of the disclosure of the application as filed. *Id.*

Here, the Office does not set forth any findings of fact to support its written description rejection. Specifically, the Office does not clearly identify the claim limitation(s) at issue. What is it about the recited DNA polymerase that is not adequately described? Is it the mutation at V93? Or is it the mutation in one of the recited exonuclease motifs? Or is it something else? Nor does the Office provide any evidence or reasoning to support its assertion that one of skill in the art would have recognized that Applicants were not in possession of the DNA polymerase recited in the claims. Accordingly, the rejection should be reversed on this ground alone.

Moreover, while the Office "acknowledges" Applicants' previously filed response and arguments, it does not respond to those rebuttal arguments or otherwise address the evidence and reasoning provided in Applicants' reply. *See* M.P.E.P. § 2163.04 ("If the record still does not demonstrate that the written description is adequate to support the claim(s), repeat the rejection under 35 U.S.C. 112, para. 1, *fully respond to applicant's rebuttal arguments, and properly treat any further showings submitted by applicant in the reply*.") (emphasis added).

Relying on the guidance provided in the specification, Applicants asserted in the

previously filed response that one of skill in the art would be able to generate other mutant Archaeal DNA polymerases with a mutation at V93. The Office does not contest this or provide any evidence to suggest otherwise.

Applicants also noted in the previously filed response that it was known in the art 1) that the exonuclease domain is conserved among DNA polymerases and comprises three conserved motifs (exo I, exo II, and exo III), and 2) that mutations in the DNA polymerase exonuclease domain result in mutant polymerases having deficient 3'-5' exonuclease activity. Thus there was a known correlation between structure (i.e., an Archaeal DNA polymerase (one of SEQ ID NOs. 83-108), including the elected invention SEQ ID NO. 89) comprising at least one mutation in an exo I, exo II, or exo III motif (or combination thereof) and function (i.e., deficient in 3'-5' exonuclease activity). The Office does not contest this finding or provide any evidence to the contrary.

Instead, while acknowledging that "applicants provide additional mutations of the disclosed polymerases that are deficient in 3'-5' exonuclease," the Office merely concludes, without any evidence or reasoning, that "these additional referred to mutants are not sufficient to adequately describe the claimed genus of any archaeal DNA polymerase deficient in 3'-5' exonuclease activity, wherein said mutant comprises at least one mutation in a exoI, exoII, or exoIII motif and another mutation at position V93 of the polymerase." Office Action at pages 5-6.

The Office also asserts:

> Applicants argument that the disclosed species of archael DNA polymerases and the disclosed mutants of SEQ ID NO: 89 are sufficient to provide a particular structure to function/activity relationship that would put one in possession of the genus of all possible mutant archael DNA polymerases with a reduced base analog detection [*sic*, deficient 3'-5' exonuclease] activity comparing [*sic*,

> comprising] a mutation in a exoI , exoII, or exoIII motif and having a mutation corresponding to V93 is not persuasive.

Office Action at page 6.

Again, the Office provides no evidence or reasoning to support these conclusory statements. Moreover, the Office mischaracterizes Applicants' previous argument. Applicants did not argue that the disclosed species, alone, are sufficient to establish a correlation between structure and function. Rather, Applicants pointed to both the disclosed species in the application and the known correlation in the art between the conserved exonuclease domain of Archaeal DNA polymerases, including SEQ ID NO. 89, and 3'-5' exonuclease activity to establish a correlation between structure and function. Specifically, Applicants argued that "given the known and disclosed correlation between the conserved, DNA polymerase exonuclease domain (structure) and its 3'-5' exonuclease activity (function), Applicant has adequately described the claimed subject matter." Response filed 30 September 2007 at page 11. As noted in the M.P.E.P., "the written description requirement for a claimed genus may be satisfied . . . by disclosure of relevant identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a *known or disclosed* correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus . . . ." MPEP §2163 (emphasis added).

Next, the Office asserts that "the specification fails to describe additional representative species of these mutant DNA polymerases by any identifying structural characteristics or properties other than the activities recited in the claims, for which no predictability of structure is apparent." Office Action at page 6. Applicants do not agree.

First, the claimed polymerase is clearly defined by characteristics "other than the

activities recited in the claims." For example, claims 1-7 are directed to an Archaeal DNA polymerase comprising an amino acid mutation at V93 and at least one amino acid mutation in the recited exonuclease motifs in an amino acid sequence selected from one of SEQ ID NOs. 83-108.

Second, contrary to the Office's unsupported assertions, there is a predictable structure for the recited function. Given the known and disclosed correlation between structure and function discussed above, the evidence indicates that one of skill in the art would recognize a predictable relationship between the recited structure (at least one mutation in the conserved exonuclease domain of the Archaeal DNA polymerases) and the recited function (deficient in 3'-5' exonuclease activity). This evidence stands unrebutted.

Finally, the Office asserts that "[g]iven this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize applicants were in possession of the claimed invention." Office Action at page 6. Applicants do not agree.

As an initial matter, as set forth in the previous response, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species **or** by disclosure of relevant identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or some combination of characteristics. *See* MPEP §2163; *see also*, *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 964, 63 USPQ2d 1609, 1613 (Fed. Cir. 2002).

Applicants argued previously that the written description requirement was satisfied in this application by either a sufficient description of a representative species or by the disclosure of

relevant identifying characteristics. In focusing on the "representative number" of species, the Office fails to address Applicants' arguments about the relevant identifying characteristics that demonstrate Applicants were in possession of the claimed invention.

Moreover, the Office provides no evidence or reasoning to support its conclusion that Applicants do not describe a representative number of species. In so doing, the Office overlooks both the level of skill and knowledge in the art. "What constitutes a 'representative number' is an inverse function of the skill and knowledge in the art." M.P.E.P. §2163. Here, the level of skill in the art is high. The Office does not contest this. Furthermore, there was a known correlation in the art between mutations in the exonuclease domain of Archaeal DNA polymerase and 3'-5' exonuclease activity. As noted in the M.P.E.P., "[s]atisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." *Id.* One of skill in the art would recognize the common features of the claimed genus as a mutation at V93 and at least one mutation in a conserved exonuclease domain (either exo I, exo II, exo III, or a combination thereof) in an Archaeal DNA polymerase selected from one of SEQ ID NOs. 83-108, and deficient 3'-5' exonuclease activity. The evidence shows that Applicants were in possession of the common features of the claimed genus. Specifically, Applicants discovered the mutation at V93 and produced V93 mutants in several Archaeal DNA polymerase species. Specification at pages 76-77. In addition, as noted above, there was a disclosed and known correlation between the conserved exonuclease domain of Archaeal DNA polymerases and 3'-5' exonuclease activity. Furthermore, the sequences of the DNA polymerases recited in the claims (SEQ ID NOs 83-108) were known. Thus, given the high level of skill in the art, the knowledge in the art,

and Applicants' disclosure, one of skill in the art would have recognized that Applicants possessed the common feature of the claimed genus and thus adequately described the same.

For these reasons, Applicants request that the Office reconsider and withdraw this written description rejection.

B. Claims 1-10 and 12-21 Are Enabled

The Office rejects claims 1-10 and 12-21 under 35 U.S.C. §112, first paragraph, alleging that the specification does not enable one of skill in the art to make and use the invention commensurate in scope with the claimed invention. Office Action at page 7. Applicants respectfully traverse this rejection.

The Office has the initial burden of establishing a *prima facie* case of lack of enablement. M.P.E.P. § 2164.04. Applicants' specification disclosing how to make and use the claimed invention must be taken as complying with 35 U.S.C. § 112, first paragraph, unless there is reason to doubt the objective truth of the disclosure. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1437, 1442 (Fed. Cir. 1995). The Office has questioned the scope of enablement provided by Applicants' specification but has not given any technical reasons to support the rejection. As stated in *In re Marzocchi*, 169 USPQ at 369 (emphasis in original):

> [I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.

Absent such evidence, the burden ***does not shift*** to the Applicants. *Id.*

The specification provides numerous examples of Archaeal DNA polymerases having a mutation at V93. *See e.g.*, Specification at page 36, lines 7-17; page 76, line 6 to page 77, line 16. The specification also provides specific examples of mutant Archaeal DNA polymerases

with deficient 3'-5' exonuclease activity, including those with a mutation at the position corresponding to D141 and/or E143 in the conserved exonuclease domain. Specification at page 33. In addition, Applicants combined the exonuclease mutants with the V93 mutants to produce mutant Archaeal DNA polymerases with deficient 3'-5' activity. Specification at page 78, lines 10-11; Figures 15-16. The Office does not provide any evidence or reasoning why the specification does not enable those disclosed mutant polymerases.

The Office acknowledges that while

> methods to produce specific variants (i.e., exo I, exoII, exoIII and mutants of V93) of a known sequence such as site specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan, producing variants as claimed by applicants (i.e., deficient in 3'-5' exonuclease activity) requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the infinite number of mutant archaeal polymerases would have the claimed property. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute undue experimentation. For example applicants state in their specification that encompassed by "archael" DNA polymerases are both the Family B/pol I-type group or the pol II group, yet it appears that applicants arguments are predominantly in support of the Family B/pol II group.

Office Action at page 8. Notably, the Office provides no evidence or reasoning to support its assertions. Applicants also do not understand the Office's reference to the "Family B/pol II group" or the reasoning relied on to support the assertions regarding the same. The specification refers to Family B/pol I and pol II polymerases but not Family B/pol II polymerases. Furthermore, any distinction between Family B/pol I and pol II polymerases overlooks the recitation in the claims that the Archaeal DNA polymerase comprises the recited mutations in an amino acid sequence selected from SEQ ID NOs. 83-108, including the elected sequence SEQ ID NO. 89.

The Office further asserts that

> [t]he specification does not establish: (A) regions of the protein structure which may be modified without effecting [*sic*, affecting] deficiencies in 3'-5' exonuclease activity; (B) the general tolerance of Archaeal Family B/pol I-type and pol II-type DNA polymerase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue of any Archaeal DNA polymerase including both Family B/pol I-type and pol II-type DNA polymerases with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Office Action at 9.

As previously argued, the specification, coupled with the knowledge in the art, provides substantial guidance as to the specific, conserved motifs within Archaeal DNA polymerases that are associated with the 3'-5' exonuclease activity of the polymerases. As explained in the specification:

> The 3'-5' exonuclease activity associated with proofreading DNA polymerases can be reduced or abolished by mutagenesis. Sequence comparisons have identified three conserved domains (exo I (DXE), II (NX_{2-3}(F/Y)D), III (YX_3D) in the 3'-5' exonuclease domain of DNA polymerases (reviewed V. Derbyshire, J.K. Pinsonneault, and C.M. Joyce, Methods Enzymol. 262, 363 (1995)).

Specification at page 32. Thus, contrary to the Office's assertions, the specification establishes that it was known in the art that specific, conserved domains are associated with 3'-5' exonuclease activity in DNA polymerases and that mutations in those domains result in diminished 3'-5' exonuclease activity. Moreover, given the known correlation between structure (the conserved exo I, II, and III motifs) and function (3'-5 exonuclease activity), the specification provides a rational and predictable scheme for modifying amino acids in the conserved exo I, exo II, and/or exo III motifs of an Archaeal DNA polymerase to generate mutant DNA polymerases having deficient 3'-5' exonuclease activity, as recited in the claims. The Office provides no evidence or reasoning to doubt these teachings in the specification and, thus, has failed to

establish a *prima facie* case of lack of enablement.

As to point (D), by reciting that the Archaeal polymerase comprises at least one mutation in one or more of the exo I, exo II or ex III motifs, the claims do provide significant guidance as to which mutant polymerases will have the desired activity, i.e., deficient 3'-5' exonuclease activity. Furthermore, methods for making the claimed mutant polymerases and screening for the recited activity were known in the art and disclosed in the specification. *See* Specification at pages 33-34, 41-44, and 48-51. Given the limited number of amino acid residues falling within the exonuclease motifs recited in the claims and the known correlation between structure and function, one of skill in the art could readily make and screen DNA polymerases other than those disclosed in the application to determine if they possess the desired activity. Thus the specification demonstrates with reasonable specificity and predictability how to make and use other potential embodiments across the full scope of the claim.

Applicants note that the test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed. *Ex parte Jackson*, 217 USPQ 804, 807 (CCPA 1982). Here, one of skill in the art, using routine *in vitro* screening assays, could readily distinguish between mutant polymerases having the desired function and those that do not and, thus, fall outside the scope of the claims. Therefore, in view of the *Wands* factors discussed above, including the working examples in the specification, the high level of skill in the art, and the state of the art itself, the experimentation involved to make and use other mutant polymerases falling within the scope of the claims, and thus practice the full scope of the pending claims,

would have been routine and well within the skill of those in the art. *See e.g.*, *Johns Hopkins Univ. v. Cellpro, Inc.*, 152 F.3d 1342, 1360, 47 USPQ2d 1705, 1719 (Fed. Cir. 1989 ("test [for undue experimentation] is not merely quantitative . . . if it is merely routine.").

The Office has not provided acceptable evidence or reasoning which is inconsistent with the specification, and, therefore, has not met the initial burden of showing that the claims are not enabled. *In re Marzocchi*, 169 USPQ at 369. Accordingly, Applicants request that this rejection be reconsidered and withdrawn.

III. Double Patenting Rejections

The Office provisionally rejects claims 1-10 and 12-21 on the grounds of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1, 3-5, 13, 15, 17-29, 31-42, 58-66 of copending Application No. 10/298,680. Office Action at pages 10-11. Applicants request that the Office hold this provisional rejection in abeyance until one of the two patent applications in question is deemed to be in condition for allowance. At that time, if the Office still believes that the claims conflict with each other, Applicants will take the appropriate action to address the possibility of double patenting. *See* M.P.E.P. §804.

IV. Conclusion

Applicants believe that all of the substantive issues raised in the Final Office Action mailed 28 February 2008 have been addressed, and all objections and rejections overcome. Accordingly, Applicants believe that this application is in condition for allowance. If the Office believes anything further is required in order to place this application in even better condition for allowance, Applicants request that their undersigned representative be contacted at the number

listed below to discuss remaining issues.

Applicants believe that no fees or petitions are required for entry of this paper. However, if any petitions are required, please grant them, and if any fees are due, please charge them to Deposit Account No. 50-3740.

Respectfully submitted,
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